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STUDIES ON THE ABSORPTION AND DISPOSITION OF ^{3}H-LABELLED TALC IN THE RAT, MOUSE, GUINEA-PIG AND RABBIT

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Abstract—The absorption and disposition of talc was studied in rats, mice and guinea-pigs, following a single oral dose of ^{3}H-labelled material. The translocation of talc in the rabbit urogenital tract was studied after single and multiple intravaginal applications. More than 95% of the dose of orally administered talc was excreted in the faeces within 3–4 days by all three species studied. Traces of radioactivity found in the urine probably reflected contamination of the samples by contact with the faeces and the presence of labile ^{3}H associated with the ^{3}H-labelled talc. No translocation of talc to the liver or kidneys was found. In the rabbit study, no translocation of talc into the ovaries was detected.

INTRODUCTION

Talc is a naturally occurring hydrous magnesium silicate with a general formula approximating to $Mg_3Si_4O_{10}(OH)_2$. It is used extensively in industry as well as having wide acceptance as a cosmetic and toiletry product. Although chemically inert, talc has been implicated in the development of tissue granulomas (Henderson, Melville-Jones, Barr & Griffiths, 1975; Migaki & Garner, 1969; Min, Gyorkey & Cain, 1974; Tye, Hashimoto & Fox, 1966), and a form of pneumoconiosis after inhalation (Miller, Tierstein, Bader, Bader & Selikoff, 1971). A report by Henderson, Joslin, Turnbull & Griffith (1971) indicated an association between cancer of the cervix and ovaries in humans and talc particles at these sites. The suggestion that there may be a link between the presence of talc particles and cancer was supported by studies on the tissues of Japanese patients with gastric cancer (Henderson, Evans, Davies & Griffiths, 1975; Matsudo, Hodgkin & Tanaka, 1974). Although the evidence presented in these studies is equivocal, the possibility of a causal relationship between particular types of tumours and the presence of talc has caused disquiet about its safety-in-use.

The development of a method for preparing ^{3}H-labelled talc (Gangolli, Crampton & Lloyd, 1973) facilitated the investigation of the biological fate of this talc preparation. In this paper, we present findings on the disposition of ^{3}H-labelled talc administered orally to rats, mice and guinea-pigs, and on the migration of talc into the urogenital systems of female rabbits.

EXPERIMENTAL

Materials. Talc (Purified, BP), supplied by Evans Medical Ltd, Liverpool, was labelled with ^{3}H as previously described (Gangolli *et al.*, 1973), using ^3H_2O with a specific activity of 500 mCi/ml. The specific activity of the talc preparation, determined by the method described below, was 100 μCi/g. The preparation conformed with the general physical characteristics of talc demonstrated by electron-microscopic and X-ray diffraction studies (J. K. Foreman, personal communication, 1972). In all the experiments, the ^{3}[H] talc preparation was administered as a suspension in aqueous glycerol jelly solution (10 mg/ml, 1 μCi/ml). This medium maintains a stable suspension of the talc particles for dosing, but rapidly dissolves *in vivo*.

Animals and diets. Female guinea-pigs of the Dunkin/Hartley strain (250–300 g body weight), male Wistar albino rats (120–150 g body weight), female mice of the LACA strain (30–40 g body weight) and female Large White rabbits (3–4 kg body weight) were used in these studies.

The rats and mice were maintained on Spillers Laboratory Small Animal Diet No. 1, and the guinea-pigs and rabbits on Oxoid Diet SG1. All animals were given both food and water *ad lib.* and kept at 20 ± 2°C. The guinea-pigs were given vitamin C supplement in the drinking-water. The rats, mice and guinea-pigs were housed individually in all-glass metabolism cages (Jencon Scientific Ltd., Hemel Hempstead, Herts). The rabbits in aluminium metabolism cages (All-Type Tools Ltd., Woolwich, London), equipped with a grid floor to retain faeces and having an inverted cone-shaped tray beneath with a hole in the apex to allow the urine to run into a collection flask.

Stability of the ^{3}H-labelled talc. ^{3}[H] Talc (30 mg, 0·3 μCi) was boiled in water (10 ml) for 30 min. The suspension was cooled and filtered through a 45-μm millipore filter and the radioactivity in the filtrate was determined. In addition two male rats were injected sc with ^{3}H-labelled talc suspension (0·1 ml, 10 mg). After 5 days, the granuloma produced at the injection site was excised and the total radioactivity was determined.

Biological disposition studies—oral administration. Three male rats were each given a single dose of ^{3}H-labelled talc by oral intubation (0·5 ml suspen-

sion/100 g body weight) providing a dose level of 50 mg talc/kg body weight. Urine and faeces were collected 24-hr intervals for 4 days and on day 10. At the end of the experimental period the liver, kidneys and gastro-intestinal tract were removed, samples of urine (0·5 ml) were assayed directly for radioactivity and the radioactivity in the faeces and tissues was determined by combustion. Three further rats were given orally six daily doses of ^{3}[H]talc (50 mg talc/kg body weight/day), and killed 10 days after the last dose. Radioactivity in excreta and tissues was determined as described for the single-dose experiment. Each of three female guinea-pigs was given a single oral dose of ^{3}H-labelled talc at a level of 25 mg/kg. Urine and faeces were collected at 24-hr intervals as in the previous experiment. After 10 days the animals were killed and liver, kidneys and gut were removed. Radioactivity in the samples was determined as described for the rat. In addition four female mice were given a single oral dose of ^{3}H-labelled talc at a level of 40 mg/kg. Two animals were killed at 6 hr and two at 24 hr. Urine and faeces were collected and the complete gastro-intestinal tract was separated from the carcasses. Radioactivity was determined in the urine, in the combined faeces and large intestine, in the combined stomach and small intestine and in the carcass.

Biological disposition studies—intravaginal administration. Three rabbits were given a single intravaginal dose of ^{3}H-labelled talc suspension (0·5 ml) and placed in metabolism cages. Urine was collected at 24-hr intervals for 3 days. The rabbits were then killed and the urogenital tract was dissected out. The total ratioactivity was determined in the urine, the ovaries, the fallopian/uterine tubes and cervix, and the vagina and bladder. A further three rabbits were given six daily doses of ^{3}H-labelled talc intravaginally, and then killed 72 hr after the final dose. The urogenital tracts were dissected out and the radioactivity was determined as in the single-dose experiment.

Radioactivity determinations. Radioactivity was measured in a Packard 2650 liquid scintillation counter and efficiency was determined by the external channels-ratio method. Urine (0·5 ml) was counted in a scintillation fluid of toluene–2-ethoxyethanol (1:1, v/v) containing 2,5-diphenyloxazole (PPO, 0·4%, v/v). Faeces, tissues and portions of talc suspension were oxidized in a Packard 306 Sample Oxidiser and the ^3H_2O produced was counted in 15 ml Monophase 40 (Packard Instruments, Des Plaines, IL, USA). Tritium recovery was 97–99%.

RESULTS

Both *in vitro* and *in vivo* levels of exchange with external hydrogen atoms were determined for the samples of ^{3}H-labelled talc used in these experiments. Less than 0·9% of the label was lost after 30 min in boiling water, and *in vivo* 97·3–99·4% of the label was recovered in the sc granulomas excised from rats 5 days after talc injections. No radioactivity was detected in the urine of these rats.

Following the oral administration of a single dose of ^{3}H talc to rats, approximately 75% of the label was recovered in the faeces within 24 hr (Table 1). Most of the radioactivity (95·8%) had been excreted after 96 hr, and only a trace of radioactivity (3200 ± 340 dpm, equivalent to 0·08% of the administered dose) remained in the gastro-intestinal tract at 240 hr. Less than 2% of the administered radioactivity was accounted for in the urine during the course of the experiment. However, there was no radioactivity in the liver or kidneys after 10 days.

In the case of rats given six daily doses of ^{3}[H]talc orally, there was no radioactivity in the day-10 faeces or in the livers of the animals at this time, although there was a trace of activity in the kidneys (less than 0·02% of the total dose).

After administration of a single oral dose of ^{3}[H]talc to guinea-pigs, almost all of the radioactivity was recovered in the faeces by 96 hr, although the activity recovered in the 24-hr faeces was substantially lower than from the rat (Table 2). Very little radioactivity appeared in the urine (less than 0·2% of the dose), and although the radioactivity remaining in the gastro-intestinal tract at 96 hr was higher than in the rat, by 10 days only a trace of activity (less than 0·03% of the dose) remained.

Following oral administration of [^{3}H]talc to mice, all of the radioactivity was found in the gastro-intestinal tract and faeces at 6 and 24 hr. No radioactivity was detected in the rest of the carcass (Table 3).

The administration of a single dose of ^{3}H-labelled talc into the rabbit vagina resulted in radioactivity in the urogenital tract being detected only at the site of adminstration after 72 hr (0·004 ± 0·001% of dose). The sensitivity of the method is such that 0·25 μg of talc could be detected. No attempt was made to quantitate the total recovery of radioactivity. Seventy-two hours after the last of six daily intravaginal doses, radioactivity was detected in the urogenital tract at the site of administration (0·035 ± 0·024% of dose)

Table 1. *Excretion of ^{3}H-labelled talc following oral administration to rats*

Time (hr)	Percentage of dose excreted* in		
	Faeces	Urine	Total
0–24	74·8 ± 8·9	1·05 ± 0·51	75·9 ± 9·1
24–48	9·5 ± 8·5	0·58 ± 0·26	10·1 ± 8·7
48–72	10·8 ± 17·2	0·06 ± 0·08	10·9 ± 17·1
72–96	0·6 ± 0·2	<0·01	0·6 ± 0·2
216–240	0·07 ± 0·02	<0·01	0·07 ± 0·02
0–96	95·8 ± 9·4	1·67 ± 0·30	97·5 ± 10·3

*Expressed as mean ± SD for three animals.

Table 2. *Excretion of ^3H-labelled talc following oral administration to guinea-pigs*

Time (hr)	Percentage of dose excreted* in		
	Faeces	Urine	Total
0–24	31·4 ± 14·4	0·2 ± 0·01	31·6 ± 14·4
24–48	39·3 ± 6·5	<0·01	39·3 ± 6·5
48–72	18·9 ± 15·8	<0·01	18·9 ± 15·8
72–96	4·8 ± 4·5	<0·01	4·8 ± 4·5
216–240	0·03 ± 0·01	<0·01	0·03 ± 0·01
0–96	94·4 ± 6·2	0·2 ± 0·01	94·6 ± 6·3

*Expressed as mean ± SD for three animals.

Table 3. *Distribution of ^3H in mice following oral administration of ^3H-labelled talc*

Time (hr)	Percentage of dose recovered* in				Total recovery (% of dose)
	Urine	Large intestine and faeces	Small intestine and stomach	Carcass	
0–6	0·66	94·8	9·0	<0·005	104·5
	0·0	96·2	7·1	<0·005	103·3
0–24	1·26	98·9	4·4	<0·005	104·6
	1·49	101·1	6·4	<0·005	109·0

*Values represent results from individual mice.

and a small amount was found associated with the cervix and fallopian/uterine tubes (0·006 ± 0·003% of dose). However, no radioactivity was found in the ovaries.

DISCUSSION

The widespread use of talc in the food industry and the consequent exposure of the general population to this material has led to concern over the possible involvement of talc in the aetiology of stomach cancer and tissue-granuloma formation. The present study has demonstrated that orally administered talc is not translocated from the gastro-intestinal tract of rats, mice or guinea-pigs, but that it is almost entirely excreted in the faeces over a period of 3–4 days. Following a single dose of ^3H-labelled talc to rat and guinea-pigs, less than 0·08 and 0·03%, respectively, of administered radioactivity remains associated with the gastro-intestinal tract after 10 days. The low level of radioactivity in the urine probably represents contamination of the samples with faeces during the separation of the excreta in the metabolism cages, and labile ^3H associated with the ^3H-labelled talc samples. However labile ^3H has been shown to represent less than 1% of the administered radioactivity.

The recent finding that ovarian tumours may contain talc particles (Henderson *et al.* 1971) has led to concern over the application of talc to the female urogenital region both as a cosmetic preparation and in association with gynaecological examination. Our study shows that talc does not migrate to the ovaries of rabbits given the material intravaginally after either single or repeated applications. Our finding that talc is not translocated from the site of administration is supported by a recent study by Wehner, Wilkerson, Cannon, Buschbom & Tanner (1977), who found that talc administered by inhalation to hamsters was not translocated from the respiratory tract, and there was no evidence of talc in the liver, kidneys or ovaries of the animals. Trace amounts of radionuclides in the urine of exposed animals were possibly due to leaching from the talc.

The results of this study suggest, therefore, that talc administered orally to rats, guinea-pigs and mice remains within the gastro-intestinal tract and is completely eliminated within 3–4 days. The study also shows that talc applied intravaginally to the rabbit does not migrate to the ovaries.

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